

REMARKS

This amendment is filed concurrent with the Continuation Prosecution Application bearing the same serial number as the parent application. A Final Office Action in the parent application was mailed September 12, 2002. This Continuing Prosecution Application under 37 CFR 1.53(d) is being filed in lieu of a Response to Final Office Action. The Preliminary Amendment is being filed to present clear and convincing evidence of the utility of the instant invention as well as arguments to overcome the other rejections set forth in the Final Office Action of September 12, 2002.

Claims 2-14 and 21 are pending in the application.

Utility rejections under 35 U.S.C. §§ 101 and 112, first paragraph:

In the Final Office Action mailed September 12, 2002, the Examiner maintained the rejection of claims 2-14 and 21 under 35 U.S.C. §§ 101 and 112, first paragraph as allegedly lacking either a specific asserted utility, credible asserted utility or a well established utility (Final Office Action, p. 2).

The rejection of claims 2-14 and 21 is improper, as the inventions of those claims have a patentable utility as set forth in the instant specification, and/or a utility well known to one of ordinary skill in the art.

The invention at issue is a polynucleotide sequence corresponding to a gene that is expressed in humans. The novel polynucleotide codes for a polypeptide demonstrated in the patent specification to be a member of the class of mitochondrial carrier proteins, whose biological functions include transport of ions and charged metabolites between the cytosol and the mitochondrial matrix. As known in the art at the time of filing, alterations in the mitochondrial electron transport chain are characteristic of malignant cells (Tab I, p. 343), and mitochondria are also known to have a central role in regulation of apoptosis, an important contributor to cancer and other cell proliferative disorders (Tab J, pp. 34-35). As such, the claimed invention has numerous practical, beneficial uses in toxicology testing, drug development, and the diagnosis of disease, none of which requires knowledge of how the polypeptide coded for by the polynucleotide actually functions. As a result of the benefits of these uses, the claimed invention already enjoys significant commercial success.

Applicants submit with this brief the declaration of Bedilion describing some of the practical uses of the claimed invention in gene and protein expression monitoring applications. The Bedilion declaration demonstrates that the positions and arguments made by the Patent Examiner with respect to the utility of the claimed polynucleotide are without merit.

The Bedilion declaration describes, in particular, how the claimed expressed polynucleotide can be used in gene-expression monitoring applications that were well-known at the time the patent application was filed, and how those applications are useful in developing drugs and monitoring their activity. Dr. Bedilion states that the claimed invention is a useful tool when employed as a highly specific probe in a cDNA microarray:

Persons skilled in the art would [have appreciated on September 23, 1997] that cDNA microarrays that contained the SEQ ID NO:19-encoding polynucleotides would be a more useful tool than cDNA microarrays that did not contain the polynucleotides in connection with conducting gene expression monitoring studies on proposed (or actual) drugs for treating cell proliferative disorders for such purposes as evaluating their efficacy and toxicity.

The Patent Examiner does not dispute that the claimed polynucleotide can be used as a probe in cDNA microarrays and used in gene expression monitoring applications. Instead, the Patent Examiner contends that the claimed polynucleotide cannot be useful without precise knowledge of its biological function. But the law never has required knowledge of biological function to prove utility. It is the claimed invention's uses, not its functions, that are the subject of a proper analysis under the utility requirement.

In any event, as demonstrated by the Bedilion declaration, the person of ordinary skill in the art can achieve beneficial results from the claimed polynucleotide in the absence of any knowledge as to the precise function of the protein encoded by it. The uses of the claimed polynucleotide in gene expression monitoring applications are in fact independent of its precise function.

I. The Applicable Legal Standard

To meet the utility requirement of sections 101 and 112 of the Patent Act, the patent applicant need only show that the claimed invention is "practically useful," *Anderson v. Natta*, 480 F.2d 1392, 1397, 178 USPQ 458 (CCPA 1973) and confers a "specific benefit" on the public. *Brenner v.*

Manson, 383 U.S. 519, 534-35, 148 USPQ 689 (1966). As discussed in a recent Court of Appeals for the Federal Circuit case, this threshold is not high:

An invention is “useful” under section 101 if it is capable of providing some identifiable benefit. See *Brenner v. Manson*, 383 U.S. 519, 534 [148 USPQ 689] (1966); *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 [24 USPQ2d 1401] (Fed. Cir. 1992) (“to violate Section 101 the claimed device must be totally incapable of achieving a useful result”); *Fuller v. Berger*, 120 F. 274, 275 (7th Cir. 1903) (test for utility is whether invention “is incapable of serving any beneficial end”).

Juicy Whip Inc. v. Orange Bang Inc., 51 USPQ2d 1700 (Fed. Cir. 1999).

While an asserted utility must be described with specificity, the patent applicant need not demonstrate utility to a certainty. In *Stiftung v. Renishaw PLC*, 945 F.2d 1173, 1180, 20 USPQ2d 1094 (Fed. Cir. 1991), the United States Court of Appeals for the Federal Circuit explained:

An invention need not be the best or only way to accomplish a certain result, and it need only be useful to some extent and in certain applications: “[T]he fact that an invention has only limited utility and is only operable in certain applications is not grounds for finding lack of utility.” *Envirotech Corp. v. Al George, Inc.*, 730 F.2d 753, 762, 221 USPQ 473, 480 (Fed. Cir. 1984).

The specificity requirement is not, therefore, an onerous one. If the asserted utility is described so that a person of ordinary skill in the art would understand how to use the claimed invention, it is sufficiently specific. See *Standard Oil Co. v. Montedison, S.p.a.*, 212 U.S.P.Q. 327, 343 (3d Cir. 1981). The specificity requirement is met unless the asserted utility amounts to a “nebulous expression” such as “biological activity” or “biological properties” that does not convey meaningful information about the utility of what is being claimed. *Cross v. Iizuka*, 753 F.2d 1040, 1048 (Fed. Cir. 1985).

In addition to conferring a specific benefit on the public, the benefit must also be “substantial.” *Brenner*, 383 U.S. at 534. A “substantial” utility is a practical, “real-world” utility. *Nelson v. Bowler*, 626 F.2d 853, 856, 206 USPQ 881 (CCPA 1980).

If persons of ordinary skill in the art would understand that there is a “well-established” utility for the claimed invention, the threshold is met automatically and the applicant need not make any showing to demonstrate utility. Manual of Patent Examination Procedure at § 706.03(a). Only if there is no “well-established” utility for the claimed invention must the applicant demonstrate the practical benefits of the invention. *Id.*

Once the patent applicant identifies a specific utility, the claimed invention is presumed to possess it. *In re Cortright*, 165 F.3d 1353, 1357, 49 USPQ2d 1464 (Fed. Cir. 1999); *In re Brana*, 51 F.3d 1560, 1566; 34 USPQ2d 1436 (Fed. Cir. 1995). In that case, the Patent Office bears the burden of demonstrating that a person of ordinary skill in the art would reasonably doubt that the asserted utility could be achieved by the claimed invention. *Id.* To do so, the Patent Office must provide evidence or sound scientific reasoning. *See In re Langer*, 503 F.2d 1380, 1391-92, 183 USPQ 288 (CCPA 1974). If and only if the Patent Office makes such a showing, the burden shifts to the applicant to provide rebuttal evidence that would convince the person of ordinary skill that there is sufficient proof of utility. *Brana*, 51 F.3d at 1566. The applicant need only prove a “substantial likelihood” of utility; certainty is not required. *Brenner*, 383 U.S. at 532.

II. Use of the claimed polynucleotides for diagnosis of conditions or diseases characterized by expression of HRM-19, for toxicology testing, and for drug discovery are sufficient utilities under 35 U.S.C. §§ 101 and 112, first paragraph

The claimed invention meets all of the necessary requirements for establishing a credible utility under the Patent Law: There are “well-established” uses for the claimed invention known to persons of ordinary skill in the art, and there are specific practical and beneficial uses for the invention disclosed in the patent application’s specification. These uses are explained, in detail, in the Bedilion declaration accompanying this brief. Objective evidence, not considered by the Patent Office, further corroborates the credibility of the asserted utilities.

A. The use of polynucleotides encoding HRM-19 for toxicology testing, drug discovery, and disease diagnosis are practical uses that confer “specific benefits” to the public

The claimed invention has specific, substantial, real-world utility by virtue of its use in toxicology testing, drug development and disease diagnosis through gene expression profiling. These uses are explained in detail in the accompanying Bedilion declaration, the substance of which is not rebutted by the Patent Examiner. There is no dispute that the claimed invention is in fact a useful tool in cDNA

microarrays used to perform gene expression analysis. That is sufficient to establish utility for the claimed polynucleotide.

In his Declaration, Dr. Bedilion explains the many reasons why a person skilled in the art reading the Lal '750 application (the great-grandparent of the Lal '787 application) on September 23, 1997 would have understood that application to disclose the claimed polynucleotide to be useful for a number of gene expression monitoring applications, *e.g.*, as a highly specific probe for the expression of that specific polynucleotide in connection with the development of drugs and the monitoring of the activity of such drugs (Bedilion Declaration at, *e.g.*, ¶¶ 10-15). Much, but not all, of Dr. Bedilion's explanation concerns the use of the claimed polynucleotide in cDNA microarrays of the type first developed at Stanford University for evaluating the efficacy and toxicity of drugs, as well as for other applications (Bedilion Declaration, ¶¶ 12 and 15).¹

In connection with his explanations, Dr. Bedilion states that the "Lal '750 specification would have led a person skilled in the art on September 23, 1997 who was using gene expression monitoring in connection with working on developing new drugs for the treatment of cell proliferative disorders [a] to conclude that a cDNA microarray that contained the SEQ ID NO:19-encoding polynucleotides would be a highly useful tool, and [b] to request specifically that any cDNA microarray that was being used for such purposes contain the SEQ ID NO:19-encoding polynucleotides" (Bedilion Declaration, ¶ 15). For example, as explained by Dr. Bedilion, "[p]ersons skilled in the art would [have appreciated on September 23, 1997] that a cDNA microarray that contained the SEQ ID NO:19-encoding polynucleotides would be a more useful tool than a cDNA microarray that did not contain the polynucleotides in connection with conducting gene expression monitoring studies on proposed (or actual) drugs for treating cell proliferative disorders for such purposes as evaluating their efficacy and toxicity." *Id.*

¹Dr. Bedilion also explained, for example, why persons skilled in the art would also appreciate, based on the Lal '750 specification, that the claimed polynucleotide would be useful in connection with developing new drugs using technology, such as Northern analysis, that predated by many years the development of the cDNA technology (Bedilion Declaration, ¶ 16).

In support of those statements, Dr. Bedilion provided detailed explanations of how cDNA technology can be used to conduct gene expression monitoring evaluations, with extensive citations to pre-September 23, 1997 publications showing the state of the art on September 23, 1997 (Bedilion Declaration, ¶¶ 10-14). While Dr. Bedilion's explanations in paragraph 15 of his Declaration include almost four pages of text and seven subparts (a)-(g), he specifically states that his explanations are not "all-inclusive." *Id.* For example, with respect to toxicity evaluations, Dr. Bedilion had earlier explained how persons skilled in the art who were working on drug development on September 23, 1997 (and for several years prior to September 23, 1997) "without any doubt" appreciated that the toxicity (or lack of toxicity) of any proposed drug was "one of the most important criteria to be evaluated in connection with the development of the drug" and how the teachings of the Lal '750 application clearly include using differential gene expression analyses in toxicity studies (Bedilion Declaration, ¶ 10).

Thus, the Bedilion Declaration establishes that persons skilled in the art reading the Lal '750 application at the time it was filed "would have wanted their cDNA microarray to have a [SEQ ID NO:19-encoding polynucleotide probe] because a microarray that contained such a probe (as compared to one that did not) would provide more useful results in the kind of gene expression monitoring studies using cDNA microarrays that persons skilled in the art have been doing since well prior to September 23, 1997" (Bedilion Declaration, ¶ 15, item (g)). This, by itself, provides more than sufficient reason to compel the conclusion that the Lal '750 application disclosed to persons skilled in the art at the time of its filing substantial, specific and credible real-world utilities for the claimed polynucleotide.

Nowhere does the Patent Examiner address the fact that, as described on pp. 49-51 of the instant application, the claimed polynucleotides can be used as highly specific probes in, for example, cDNA microarrays – probes that without question can be used to measure both the existence and amount of complementary RNA sequences known to be the expression products of the claimed polynucleotides. The claimed invention is not, in that regard, some random sequence whose value as a probe is speculative or would require further research to determine!

Given the fact that the claimed polynucleotide is known to be expressed, its utility as a measuring and analyzing instrument for expression levels is as indisputable as a scale's utility for

measuring weight. This use as a measuring tool, regardless of how the expression level data ultimately would be used by a person of ordinary skill in the art, by itself demonstrates that the claimed invention provides an identifiable, real-world benefit that meets the utility requirement. *Raytheon v. Roper*, 724 F.2d 951, (Fed. Cir. 1983) (claimed invention need only meet one of its stated objectives to be useful); *In re Cortwright*, 165 F.3d 1353, 1359 (Fed. Cir. 1999) (how the invention works is irrelevant to utility); MPEP § 2107 (“Many research tools such as gas chromatographs, screening assays, and nucleotide sequencing techniques have a clear, specific, and unquestionable utility (e.g., they are useful in analyzing compounds)” (emphasis added)).

Though Applicants need not so prove to demonstrate utility, there can be no reasonable dispute that persons of ordinary skill in the art have numerous uses for information about relative gene expression including, for example, understanding the effects of a potential drug for treating cell proliferative disorders. Because the patent application states explicitly that the claimed polynucleotide is known to be expressed in cells and tissues associated with cell proliferation, cancer, and the immune response (see the specification at p. 18, line 28), and expresses a protein that is a member of a class (mitochondrial carrier proteins) known to be associated with diseases such as cancer, there can be no reasonable dispute that a person of ordinary skill in the art could put the claimed invention to such use. In other words, the person of ordinary skill in the art can derive more information about a potential cancer drug candidate or potential toxin with the claimed invention than without it (see Bedilion Declaration at, e.g., ¶ 15, subparts (e)-(g)).

The Bedilion Declaration shows that a number of pre-September 23, 1997 publications confirm and further establish the utility of cDNA microarrays in a wide range of drug development gene expression monitoring applications at the time the Lal '750 application was filed (Bedilion Declaration ¶¶ 10-14; Bedilion Exhibits A-G). Indeed, Brown and Shalon U.S. Patent No. 5,807,522 (the Brown '522 patent, Bedilion Exhibit D), which issued from a patent application filed in June 1995 and was effectively published on December 29, 1995 as a result of the publication of a PCT counterpart application, shows that the Patent Office recognizes the patentable utility of the cDNA technology developed in the early to mid-1990s. As explained by Dr. Bedilion, among other things (Bedilion Declaration, ¶ 12):

The Brown '522 patent further teaches that the "[m]icroarrays of immobilized nucleic acid sequences prepared in accordance with the invention" can be used in "numerous" genetic applications, including "monitoring of gene expression" applications (see Bedilion Tab D at col. 14, lines 36-42). The Brown '522 patent teaches (a) monitoring gene expression (i) in different tissue types, (ii) in different disease states, and (iii) in response to different drugs, and (b) that arrays disclosed therein may be used in toxicology studies (see Bedilion Tab D at col. 15, lines 13-18 and 52-58 and col. 18, lines 25-30).

Literature reviews published shortly after the filing of the Lal '750 application describing the state of the art further confirm the claimed invention's utility. Rockett et al. confirm, for example, that the claimed invention is useful for differential expression analysis regardless of how expression is regulated:

Despite the development of multiple technological advances which have recently brought the field of gene expression profiling to the forefront of molecular analysis, recognition of the importance of differential gene expression and characterization of differentially expressed genes has existed for many years.

* * *

Although differential expression technologies are applicable to a broad range of models, perhaps their most important advantage is that, in most cases, absolutely no prior knowledge of the specific genes which are up- or down-regulated is required.

* * *

Whereas it would be informative to know the identity and functionality of all genes up/down regulated by . . . toxicants, this would appear a longer term goal However, the current use of gene profiling yields a *pattern* of gene changes for a xenobiotic of unknown toxicity which may be matched to that of well characterized toxins, thus alerting the toxicologist to possible *in vivo* similarities between the unknown and the standard, thereby providing a platform for more extensive toxicological examination. (emphasis added)

Rockett et al., Differential gene expression in drug metabolism and toxicology: practicalities, problems and potential, 29 Xenobiotica No. 7, 655 (1999) (Reference No. 1, enclosed).

In a pre-September 23, 1997 article, Lashkari et al. state explicitly that sequences that are merely “predicted” to be expressed (predicted Open Reading Frames, or ORFs) – the claimed invention in fact is known to be expressed – have numerous uses:

Efforts have been directed toward the amplification of each predicted ORF or any other region of the genome ranging from a few base pairs to several kilobase pairs. There are many uses for these amplicons– they can be cloned into standard vectors or specialized expression vectors, or can be cloned into other specialized vectors such as those used for two-hybrid analysis. The amplicons can also be used directly by, for example, arraying onto glass for expression analysis, for DNA binding assays, or for any direct DNA assay.

Lashkari et al., Whole genome analysis: Experimental access to all genome sequenced segments through larger-scale efficient oligonucleotide synthesis and PCR, 94 Proc. Nat. Acad. Sci. 8945 (Aug. 1997) (Reference No. 2, enclosed) (emphasis added).

B. The use of nucleic acids coding for proteins expressed by humans as tools for toxicology testing, drug discovery, and the diagnosis of disease is now “well-established”

The technologies made possible by expression profiling and the DNA tools upon which they rely are now well-established. The technical literature recognizes not only the prevalence of these technologies, but also their unprecedented advantages in drug development, testing and safety assessment. These technologies include toxicology testing, as described by Bedilion in his declaration.

Toxicology testing is now standard practice in the pharmaceutical industry. See, *e.g.*, John C. Rockett et al., *supra*:

Knowledge of toxin-dependent regulation in target tissues is not solely an academic pursuit as much interest has been generated in the pharmaceutical industry to harness this technology in the early identification of toxic drug candidates, thereby shortening the developmental process and contributing substantially to the safety assessment of new drugs.

To the same effect are several other scientific publications, including Emile F. Nuwaysir et al., Microarrays and Toxicology: The Advent of Toxicogenomics, 24 Molecular Carcinogenesis 153 (1999) (Reference No. 3, enclosed); Sandra Steiner and N. Leigh Anderson, Expression profiling in

toxicology -- potentials and limitations, 112-13 Toxicology Letters 467 (2000) (Reference No. 4, enclosed).

Nucleic acids useful for measuring the expression of whole classes of genes are routinely incorporated for use in toxicology testing. Nuwaysir et al. describes, for example, a Human ToxChip comprising 2089 human clones, which were selected

for their well-documented involvement in basic cellular processes as well as their responses to different types of toxic insult. Included on this list are DNA replication and repair genes, apoptosis genes, and genes responsive to PAHs and dioxin-like compounds, peroxisome proliferators, estrogenic compounds, and oxidant stress. Some of the other categories of genes include transcription factors, oncogenes, tumor suppressor genes, cyclins, kinases, phosphatases, cell adhesion and motility genes, and homeobox genes. Also included in this group are 84 housekeeping genes, whose hybridization intensity is averaged and used for signal normalization of the other genes on the chip.

See also Table 1 of Nuwaysir et al. (listing additional classes of genes deemed to be of special interest in making a human toxicology microarray). Note in particular that the list of genes of special interest for toxicology testing includes apoptosis genes, and that mitochondria are known to have a central role in regulation of apoptosis (see Tab J, pp. 34-35).

The more genes that are available for use in toxicology testing, the more powerful the technique. "Arrays are at their most powerful when they contain the entire genome of the species they are being used to study." John C. Rockett and David J. Dix, Application of DNA Arrays to Toxicology, 107 Environ. Health Perspec. 681, No. 8 (1999) (Reference No. 6, enclosed). Control genes are carefully selected for their stability across a large set of array experiments in order to best study the effect of toxicological compounds. See attached email (Reference No. 6, enclosed) from the primary investigator on the Nuwaysir paper, Dr. Cynthia Afshari, to an Incyte employee, dated July 3, 2000, as well as the original message to which she was responding, indicating that even the expression of carefully selected control genes can be altered. Thus, there is no expressed gene which is irrelevant to screening for toxicological effects, and all expressed genes have a utility for toxicological screening.

In fact, the potential benefit to the public, in terms of lives saved and reduced health care costs, are enormous. Recent developments provide evidence that the benefits of this information are already beginning to manifest themselves. Examples include the following:

- In 1999, CV Therapeutics, an Incyte collaborator, was able to use Incyte gene expression technology, information about the structure of a known transporter gene, and chromosomal mapping location, to identify the key gene associated with Tangiers disease. This discovery took place over a matter of only a few weeks, due to the power of these new genomics technologies. The discovery received an award from the American Heart Association as one of the top 10 discoveries associated with heart disease research in 1999.
- In an April 9, 2000, article published by the Bloomberg news service, an Incyte customer stated that it had reduced the time associated with target discovery and validation from 36 months to 18 months, through use of Incyte's genomic information database. Other Incyte customers have privately reported similar experiences. The implications of this significant saving of time and expense for the number of drugs that may be developed and their cost are obvious.
- In a February 10, 2000, article in the *Wall Street Journal*, one Incyte customer stated that over 50 percent of the drug targets in its current pipeline were derived from the Incyte database. Other Incyte customers have privately reported similar experiences. By doubling the number of targets available to pharmaceutical researchers, Incyte genomic information has demonstrably accelerated the development of new drugs.

Because the Patent Examiner failed to address or consider the "well-established" utilities for the claimed invention in toxicology testing, drug development, and the diagnosis of disease, the Examiner's rejections should be overturned regardless of their merit.

C. The fact that the claimed polynucleotide encodes a protein in the mitochondrial carrier protein family also demonstrates utility

In addition to having substantial, specific and credible utilities in numerous gene expression monitoring applications, it is undisputed that the claimed polynucleotide encodes a protein having the sequence shown as SEQ ID NO:19 in the patent application and referred to as HRM-19 in that application. Applicants have demonstrated that HRM-19 is a member of the mitochondrial carrier protein family, and that the mitochondrial carrier family of proteins includes carriers involved in the transport of ions and charged metabolites between the cytosol and the mitochondrial matrix.

It is undisputed, and readily apparent from the patent application, that the polypeptide encoded for by the claimed polynucleotide shares more than 35% amino acid sequence identity over 351 amino acid residues with *C. elegans* C16C10 (g577542) (Lal '750 application, p. 18, lines 27-28; Table 1), a putative mitochondrial carrier protein. In addition, HRM-19 contains a mitochondrial carrier motif, P₃₁LDVVKVRL (Lal '750 application, p. 18, lines 26-27). This is more than enough homology to demonstrate a reasonable probability that the utility of the mitochondrial carrier protein family can be imputed to the claimed invention (through the polypeptide it encodes). The Examiner asserts that “[i]n most cases, such a degree of homology does not allow the prediction of specific function” (Final Office Action, p. 7). To the contrary, it is well-known that the probability that two unrelated polypeptides share more than 30% sequence homology over 150 amino acid residues is exceedingly small. See Brenner et al., Proc. Natl. Acad. Sci. 95:6073-78 (1998) (Reference No. 7, enclosed). Given homology in excess of 30% over many more than 150 amino acid residues, the probability that the polypeptide encoded for by the claimed polynucleotide is related to the *C. elegans* mitochondrial carrier protein is, accordingly, very high.

The Patent Examiner does not dispute any of the facts set forth in the previous paragraph. Neither does the Patent Examiner dispute that, if a polynucleotide encodes for a protein that has a substantial, specific and credible utility, then it follows that the polynucleotide also has a substantial, specific and credible utility.

The Examiner must accept the applicant’s demonstration that the polypeptide encoded by the claimed invention is a member of the mitochondrial carrier protein family and that utility is proven by a reasonable probability unless the Examiner can demonstrate through evidence or sound scientific reasoning that a person of ordinary skill in the art would doubt utility. *See In re Langer*, 503 F.2d 1380, 1391-92, 183 USPQ 288 (CCPA 1974). The Examiner has not provided sufficient evidence or sound scientific reasoning to the contrary.

Nor has the Examiner provided any evidence that any member of the mitochondrial carrier protein family, let alone a substantial number of those members, is not useful. In such circumstances, the only reasonable inference is that the polypeptide encoded by the claimed invention must be, like the other members of the mitochondrial carrier protein family, useful.

D. Objective evidence corroborates the utilities of the claimed invention

There is, in fact, no restriction on the kinds of evidence a Patent Examiner may consider in determining whether a “real-world” utility exists. Indeed, “real-world” evidence, such as evidence showing actual use or commercial success of the invention, can demonstrate conclusive proof of utility. *Raytheon v. Roper*, 220 USPQ2d 592 (Fed. Cir. 1983); *Nestle v. Eugene*, 55 F.2d 854, 856, 12 USPQ 335 (6th Cir. 1932). Indeed, proof that the invention is made, used or sold by any person or entity other than the patentee is conclusive proof of utility. *United States Steel Corp. v. Phillips Petroleum Co.*, 865 F.2d 1247, 1252, 9 USPQ2d 1461 (Fed. Cir. 1989).

Over the past several years, a vibrant market has developed for databases containing all expressed genes (along with the polypeptide translations of those genes), in particular genes having medical and pharmaceutical significance such as the instant sequence. (Note that the value in these databases is enhanced by their completeness, but each sequence in them is independently valuable.) The databases sold by Applicants’ assignee, Incyte, include exactly the kinds of information made possible by the claimed invention, such as tissue and disease associations. Incyte sells its database containing the claimed sequence and millions of other sequences throughout the scientific community, including to pharmaceutical companies who use the information to develop new pharmaceuticals.

Both Incyte’s customers and the scientific community have acknowledged that Incyte’s databases have proven to be valuable in, for example, the identification and development of drug candidates. As Incyte adds information to its databases, including the information that can be generated only as a result of Incyte’s discovery of the claimed polynucleotide and its use of that polynucleotide on cDNA microarrays, the databases become even more powerful tools. Thus the claimed invention adds more than incremental benefit to the drug discovery and development process.

Customers can, moreover, purchase the claimed polynucleotide directly from Incyte, saving the customer the time and expense of isolating and purifying or cloning the polynucleotide for research uses such as those described *supra*.

III. The Patent Examiner's Rejections Are Without Merit

Rather than responding to the evidence demonstrating utility, the Examiner attempts to dismiss it altogether by arguing that the disclosed and well-established utilities for the claimed polynucleotide are not "specific, substantial, and credible" utilities (Final Office Action at p. 6). The Examiner is incorrect both as a matter of law and as a matter of fact.

A. The precise biological role or function of an expressed polynucleotide is not required to demonstrate utility

The Patent Examiner's primary rejection of the claimed invention is based on the ground that, without information as to the precise "biological role" of the claimed invention, the claimed invention's utility is not sufficiently specific. According to the Examiner, it is not enough that a person of ordinary skill in the art could use and, in fact, would want to use the claimed invention either by itself or in a cDNA microarray to monitor the expression of genes for such applications as the evaluation of a drug's efficacy and toxicity. The Examiner would require, in addition, that the applicant provide a specific and substantial interpretation of the results generated in any given expression analysis.

It may be that specific and substantial interpretations and detailed information on biological function are necessary to satisfy the requirements for publication in some technical journals, but they are not necessary to satisfy the requirements for obtaining a United States patent. The relevant question is not, as the Examiner would have it, whether it is known how or why the invention works, *In re Cortwright*, 165 F.3d 1353, 1359 (Fed. Cir. 1999), but rather whether the invention provides an "identifiable benefit" in presently available form. *Juicy Whip Inc. v. Orange Bang Inc.*, 185 F.3d 1364, 1366 (Fed. Cir. 1999). If the benefit exists, and there is a substantial likelihood the invention provides the benefit, it is useful. There can be no doubt, particularly in view of the Bedilion Declaration (at, e.g., ¶¶ 10 and 15, Bedilion), that the present invention meets this test.

The threshold for determining whether an invention produces an identifiable benefit is low. *Juicy Whip*, 185 F.3d at 1366. Only those utilities that are so nebulous that a person of ordinary skill in the art would not know how to achieve an identifiable benefit and, at least according to the PTO guidelines, so-called "throwaway" utilities that are not directed to a person of ordinary skill in the art at

all, do not meet the statutory requirement of utility. Utility Examination Guidelines, 66 Fed. Reg. 1092 (Jan. 5, 2001).

Knowledge of the biological function or role of a biological molecule has never been required to show real-world benefit. In its most recent explanation of its own utility guidelines, the PTO acknowledged so much (66 F.R. at 1095):

[T]he utility of a claimed DNA does not necessarily depend on the function of the encoded gene product. A claimed DNA may have specific and substantial utility because, *e.g.*, it hybridizes near a disease-associated gene or it has gene-regulating activity.

By implicitly requiring knowledge of biological function for any claimed nucleic acid, the Examiner has, contrary to law, elevated what is at most an evidentiary factor into an absolute requirement of utility. Rather than looking to the biological role or function of the claimed invention, the Examiner should have looked first to the benefits it is alleged to provide.

B. Membership in a class of useful products can be proof of utility

Despite the uncontradicted evidence that the claimed polynucleotide encodes a polypeptide in the mitochondrial carrier protein family, the Examiner refused to impute the utility of the members of the mitochondrial carrier protein family to HRM-19. In the Final Office Action, the Patent Examiner takes the position that, unless Applicants can identify which particular biological function within the class of mitochondrial carrier proteins is possessed by HRM-19, such as the specific substrate for the carrier, utility cannot be imputed (Final Office Action, p. 3). To demonstrate utility by membership in the class of mitochondrial carrier proteins, the Examiner in effect would require that all mitochondrial carrier proteins possess a “common” utility.

There is no such requirement in the law. In order to demonstrate utility by membership in a class, the law requires only that the class not contain a substantial number of useless members. So long as the class does not contain a substantial number of useless members, there is sufficient likelihood that the claimed invention will have utility, and a rejection under 35 U.S.C. § 101 is improper. That is true regardless of how the claimed invention ultimately is used and whether or not the members of the class

possess one utility or many. See *Brenner v. Manson*, 383 U.S. 519, 532 (1966); *Application of Kirk*, 376 F.2d 936, 943 (CCPA 1967).

Membership in a “general” class is insufficient to demonstrate utility only if the class contains a sufficient number of useless members such that a person of ordinary skill in the art could not impute utility by a substantial likelihood. There would be, in that case, a substantial likelihood that the claimed invention is one of the useless members of the class. In the few cases in which class membership did not prove utility by substantial likelihood, the classes did in fact include predominately useless members. E.g., *Brenner* (man-made steroids); *Kirk* (same); *Natta* (man-made polyethylene polymers).

The Examiner addresses HRM-19 as if the general class in which it is included is not the mitochondrial carrier protein family, but rather all polynucleotides or all polypeptides, including the vast majority of useless theoretical molecules not occurring in nature, and thus not pre-selected by nature to be useful. While these “general classes” may contain a substantial number of useless members, the mitochondrial carrier protein family does not. The mitochondrial carrier protein family is sufficiently specific to rule out any reasonable possibility that HRM-19 would not also be useful like the other members of the family.

Because the Examiner has not presented any evidence that the mitochondrial carrier class of transporter proteins has any, let alone a substantial number, of useless members, the Examiner must conclude that there is a “substantial likelihood” that the HRM-19 encoded by the claimed polynucleotide is useful. It follows that the claimed polynucleotides encoding HRM-19 also are useful.

Even if the Examiner's “common utility” criterion were correct – and it is not – the mitochondrial carrier protein family would meet it. It is undisputed that known members of the mitochondrial carrier protein family are transporter proteins that transport ions and charged metabolites between the cytosol and the mitochondrial matrix. A person of ordinary skill in the art need not know any more about how the claimed invention functions in transport between the cytosol and the mitochondrial matrix to use it, and the Examiner presents no evidence to the contrary. Instead, the Examiner makes the conclusory observation that a person of ordinary skill in the art would need to know whether, for example, any given mitochondrial carrier protein transports a specific substrate. The Examiner then goes on to

assume that the only use for HRM-19 absent knowledge as to how the mitochondrial carrier protein actually works is further study of HRM-19 itself.

Not so. As demonstrated by Applicants, knowledge that HRM-19 is a mitochondrial carrier protein is more than sufficient to make it useful for the diagnosis and treatment of cell proliferative disorders. Indeed, HRM-19 has been shown to be expressed in cancer cells (specification, p. 18, line 28). The Examiner must accept these facts to be true unless the Examiner can provide evidence or sound scientific reasoning to the contrary. But the Examiner has not done so.

C. Because the uses of polynucleotides encoding HRM-19 in toxicology testing, drug discovery, and disease diagnosis are practical uses beyond mere study of the invention itself, the claimed invention has substantial utility.

The PTO's rejection of the claims at issue is tantamount to an assertion that the use of an invention as a tool for research is not a "substantial" use. Because the PTO's rejection assumes a substantial overstatement of the law, and is incorrect in fact, it must be overturned.

There is no authority for the proposition that use as a tool for research is not a substantial utility. Indeed, the Patent Office has recognized that just because an invention is used in a research setting does not mean that it lacks utility (MPEP § 2107):

Many research tools such as gas chromatographs, screening assays, and nucleotide sequencing techniques have a clear, specific and unquestionable utility (e.g., they are useful in analyzing compounds). An assessment that focuses on whether an invention is useful only in a research setting thus does not address whether the specific invention is in fact "useful" in a patent sense. Instead, Office personnel must distinguish between inventions that have a specifically identified utility and inventions whose specific utility requires further research to identify or reasonably confirm.

The Patent Office's actual practice has been, at least until the present, consistent with that approach. It has routinely issued patents for inventions whose only use is to facilitate research, such as DNA ligases. These are acknowledged by the PTO's Training Materials themselves to be useful, as well as DNA sequences used, for example, as markers.

Only a limited subset of research uses are not "substantial" utilities: those in which the only known use for the claimed invention is to be an **object** of further study, thus merely inviting further research. This follows from *Brenner*, in which the U.S. Supreme Court held that a process for making

a compound does not confer a substantial benefit where the only known use of the compound was to be the object of further research to determine its use. *Id.* at 535. Similarly, in *Kirk*, the Court held that a compound would not confer substantial benefit on the public merely because it might be used to synthesize some other, unknown compound that would confer substantial benefit. *Kirk*, 376 F.2d at 940, 945 (“What Applicants are really saying to those in the art is take these steroids, experiment, and find what use they do have as medicines.”). Nowhere do those cases state or imply, however, that a material cannot be patentable if it has some other beneficial use in research.

As used in toxicology testing, drug discovery, and disease diagnosis, the claimed invention has a beneficial use in research other than studying the claimed invention or its protein products. It is a tool, rather than an object, of research. The data generated in gene expression monitoring using the claimed invention as a tool is **not** used merely to study the claimed polynucleotide itself, but rather to study properties of tissues, cells, and potential drug candidates and toxins. Without the claimed invention, the information regarding the properties of tissues, cells, drug candidates and toxins is less complete.

[Bedilion Declaration at ¶ 15.]

The claimed invention has numerous additional uses as a research tool, each of which alone is a “substantial utility.” These include use of the claimed polynucleotides in disease diagnosis (specification, pp. 47-49), expression profiling and monitoring the activities of therapeutic agents (specification, pp. 49-51), and genomic mapping (specification, pp. 51-52).

D. The Patent Examiner failed to demonstrate that a person of ordinary skill in the art would reasonably doubt the utility of the claimed invention

In response to Applicants’ identification of HRM-19 as a mitochondrial transport protein, the Examiner has asserted that it is allegedly “nearly impossible from sequence homology alone to attribute a specific and substantial function for the protein” (Final Office Action, p. 3). The Examiner further asserts in response to the acknowledged 35% amino acid identity between HRM-19 and the *C. elegans* putative mitochondrial carrier C16C10 that “[i]n most cases, such degree of homology does not allow the prediction of specific function” (Final Office Action, p. 7). Applicants respectfully note that the Examiner has provided **no evidence** for this assertion.

Applicants further note that the Brenner reference discloses that the probability that two unrelated polypeptides share more than 30% sequence homology over 150 amino acid residues is exceedingly small. (Brenner, p. 6076). Given homology in excess of 30% over many more than 150 amino acid residues, the probability that the HRM-19 polypeptide encoded for by the claimed polynucleotide is related to the *C. elegans* mitochondrial carrier protein is, accordingly, very high. Thus the known art indicates that the acknowledged homology between HRM-19 and the *C. elegans* mitochondrial carrier protein would in fact be expected to indicate a related function for the two proteins.

The Examiner also stated that additional data to support a specific function “would include the number of the specific domains associated with said function, and location of highly conserved charge-pairs” (Final Office Action, p. 3). Applicants disclosed in the specification on page 18, lines 26-27, that the amino acid sequence of HRM-19, has a specific motif characteristic of a mitochondrial carrier protein. Furthermore, as shown in the Declaration of Preeti Lal, submitted September 3, 2002, the HRM-19 protein structure indicates the presence of four mitochondrial carrier domains, six potential transmembrane spanning regions, a likely mitochondrial localization domain, and three regions with reasonable homology to putative mitochondrial energy-transfer signature motifs present in known uncoupling protein functional family members. Therefore, the Declaration and the references attached with the Declaration provide evidentiary support that one skilled in the art would more likely than not concur with Applicants’ asserted functional characterization of HRM-19 as a mitochondrial carrier protein.

The Examiner asserts that the specification did not assert that HRM-19 is a mitochondrial carrier protein but only that it has one mitochondrial carrier motif which “does not necessarily render the protein a mitochondrial carrier (Final Office Action, p. 7), and that the *C. elegans* homolog is only a “putative” carrier. Both facts taken together, however, would lead one of skill in the art to believe that HRM-19 is in fact a mitochondrial carrier, a fact reinforced by the Lal Declaration. New post-filing evidence provided in the Lal Declaration, such as the Yu article which provides experimental evidence that HRM-19 is a mitochondrial carrier protein, serve to **confirm** what was previously asserted.

The Lal Declaration also demonstrated that the transcripts for HRM-19 were significantly, differentially, up-regulated (overexpressed) in lung tissue samples from cancer patients as compared to matched normal samples from the same patient. Therefore, HRM-19, and the cDNA encoding it, are of diagnostic use in detecting lung cancers.

The Examiner asserts in response that the utility of SEQ ID NO:19 in diagnosis of lung cancer is allegedly not asserted in the specification as filed (Final Office Action, p. 7). Applicants respectfully direct the Examiner's attention to the specification at, for example, p. 18, lines 27-28, wherein the specification discloses that sequences encoding HRM-19 are found in cDNA libraries associated with cell proliferation and cancer. The specification further states that polynucleotides encoding HRM may be used for the diagnosis of cancers, including cancers of the lung (specification, p. 47, lines 24-28). The use of polynucleotides encoding HRM to detect cancer, and the association of increased amounts of transcript with cancer is further disclosed in the specification at, for example, p. 48, lines 7-16, and p. 48, line 29 through p. 49, line 1. The fact that the specification refers to HRMs in general and not HRM-19 in these instances is not relevant, because as discussed in greater detail above, an invention need not have a unique utility to be useful.

Furthermore, as discussed in the Bedilion declaration, pre-September 1997 articles known in the art at the time of filing of the Lal '750 specification point to the role of mitochondrial carrier proteins, such as HRM-19, in cell proliferative disorders (Bedilion Declaration, ¶ 15(f)). Thus, one of ordinary skill in the art would reasonably expect polynucleotides encoding HRM-19 to be useful in the diagnosis of cancers, including lung cancer.

IV. By Requiring the Patent Applicant to Assert a Particular or Unique Utility, the Patent Examination Utility Guidelines and Training Materials Applied by the Patent Examiner Misstate the Law

There is an additional, independent reason to overturn the rejections: to the extent the rejections are based on Revised Interim Utility Examination Guidelines (64 FR 71427, December 21, 1999), the final Utility Examination Guidelines (66 FR 1092, January 5, 2001) and/or the Revised Interim Utility Guidelines Training Materials (USPTO Website www.uspto.gov, March 1, 2000), the Guidelines and Training Materials are themselves inconsistent with the law.

The Training Materials, which direct the Examiners regarding how to apply the Utility Guidelines, address the issue of specificity with reference to two kinds of asserted utilities: “specific” utilities which meet the statutory requirements, and “general” utilities which do not. The Training Materials define a “specific utility” as follows:

A [specific utility] is *specific* to the subject matter claimed. This contrasts to *general* utility that would be applicable to the broad class of invention. For example, a claim to a polynucleotide whose use is disclosed simply as “gene probe” or “chromosome marker” would not be considered to be specific in the absence of a disclosure of a specific DNA target. Similarly, a general statement of diagnostic utility, such as diagnosing an unspecified disease, would ordinarily be insufficient absent a disclosure of what condition can be diagnosed.

The Training Materials distinguish between “specific” and “general” utilities by assessing whether the asserted utility is sufficiently “particular,” *i.e.*, unique (Training Materials at p.52) as compared to the “broad class of invention.” (In this regard, the Training Materials appear to parallel the view set forth in Stephen G. Kunin, Written Description Guidelines and Utility Guidelines, 82 J.P.T.O.S. 77, 97 (Feb. 2000) (“With regard to the issue of specific utility the question to ask is whether or not a utility set forth in the specification is *particular* to the claimed invention.”)).

Such “unique” or “particular” utilities never have been required by the law. To meet the utility requirement, the invention need only be “practically useful,” *Natta*, 480 F.2d 1 at 1397, and confer a “specific benefit” on the public. *Brenner*, 383 U.S. at 534. Thus, incredible “throwaway” utilities, such as trying to “patent a transgenic mouse by saying it makes great snake food,” do not meet this standard. Karen Hall, Genomic Warfare, *The American Lawyer* 68 (June 2000) (quoting John Doll, Chief of the Biotech Section of USPTO).

This does not preclude, however, a general utility, contrary to the statement in the Training Materials where “specific utility” is defined (page 5). Practical real-world uses are not limited to uses that are unique to an invention. The law requires that the practical utility be “definite,” not particular. *Montedison*, 664 F.2d at 375. Appellant is not aware of any court that has rejected an assertion of utility on the grounds that it is not “particular” or “unique” to the specific invention. Where courts have found utility to be too “general,” it has been in those cases in which the asserted utility in the patent disclosure was not a practical use that conferred a specific benefit. That is, a person of ordinary skill in the art would have been left to guess as to how to benefit at all from the invention. In *Kirk*, for

example, the CCPA held the assertion that a man-made steroid had “useful biological activity” was insufficient where there was no information in the specification as to how that biological activity could be practically used. *Kirk*, 376 F.2d at 941.

The fact that an invention can have a particular use does not provide a basis for requiring a particular use. *See Brana, supra* (disclosure describing a claimed antitumor compound as being homologous to an antitumor compound having activity against a “particular” type of cancer was determined to satisfy the specificity requirement). “Particularity” is not and never has been the *sine qua non* of utility; it is, at most, one of many factors to be considered.

As described *supra*, broad classes of inventions can satisfy the utility requirement so long as a person of ordinary skill in the art would understand how to achieve a practical benefit from knowledge of the class. Only classes that encompass a significant portion of nonuseful members would fail to meet the utility requirement. *Supra* § II.B.2 (*Montedison*, 664 F.2d at 374-75).

The Training Materials fail to distinguish between broad classes that convey information of practical utility and those that do not, lumping all of them into the latter, unpatentable category of “general” utilities. As a result, the Training Materials paint with too broad a brush. Rigorously applied, they would render unpatentable whole categories of inventions that heretofore have been considered to be patentable and that have indisputably benefitted the public, including the claimed invention. *See supra* § II.B. Thus the Training Materials cannot be applied consistently with the law.

V. To the Extent the Rejection of the Patented Invention under 35 U.S.C. § 112, First Paragraph, Is Based on the Improper Rejection for Lack of Utility under 35 U.S.C. § 101, it Must Be Reversed.

The rejection set forth in the Office Action is based on the assertions discussed above, i.e., that the claimed invention lacks patentable utility. To the extent that the rejection under § 112, first paragraph, is based on the improper allegation of lack of patentable utility under § 101, it fails for the same reasons.

CONCLUSION

In light of the above remarks, Applicants submit that the present application is fully in condition for allowance, and request that the Examiner withdraw the outstanding rejections. Early notice to that effect is earnestly solicited.

If the Examiner contemplates other action, or if a telephone conference would expedite allowance of the claims, Applicants invite the Examiner to contact Applicants' Attorney at (650) 855-0555.

A CPA filing fee is due as set out on the CPA filing request form. It is believed that no additional fees are due, but should other fees be due, the Commissioner is hereby authorized to charge Incyte Genomics, Inc. Deposit Account No. **09-0108**.

Respectfully submitted,
INCYTE GENOMICS, INC.

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Barrie D. Greene
Barrie D. Greene
Reg. No. 46,740
Direct Dial Telephone: (650) 621-7576

3160 Porter Drive
Palo Alto, California 94304
Phone: (650) 855-0555
Fax: (650) 849-8886